UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/147,490	05/13/99	MENDELSOHN	F 016786/0215

HM12/1019

FOLEY & LARDNER
3000 K STREET NW SUITE 500
PO BOX 25696
WASHINGTON DC 20007-8696

EXAMINER	
TURNER, S	
ART UNIT	PAPER NUMBER
1647	19

DATE MAILED: 10/19/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/147,490	Applicant(s) Mendelsohn et al
	Examiner Sharon L. Turner, Ph.D.	Art Unit 1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *8-2-01*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *2, 3, 6-9, and 11-27* is/are pending in the application.

4a) Of the above, claim(s) *2, 3, 6-9, 11-17, 18* and 25-27* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *18-24* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *2, 3, 6-9, and 11-27* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

Response to Amendment

1. The amendment filed 8-2-01 has been entered into the record and has been fully considered.

2. Claims 1, 4, 5 and 10 are canceled. Claims 2, 3, 6-9, and 11-27 are pending.

3. The formal drawings (1-15) submitted 8-2-01 have been forwarded to the draftsman for review.

4. Applicant's election with traverse of Group I, claims 1, 4, 5 and 10 in Paper No. 7 was previouly acknowledged. Applicant's continued traversal of 8-2-01 is on the ground(s) that unity exists between Group I and III. In particular applicants argue that the technical feature is "neuroactive peptides" as recited in the claims and that in the office action the examiner recognized that Group I was drawn to the first technical feature and that Group III was drawn to the second method of using the first technical feature. Applicant's argue that the lack of novelty of the neuroactive peptide recited is not relevant to determine unity of invention in this case. Applicant's point out the species election made by the examiner and conclude that because there exist "common" species that share biological activity and conditions that there is a single general inventive concept which is linked and forms unity of invention as a novel "use". This is not found persuasive because the special technical feature of the neuroactive peptide comprising SEQ ID NO:1 is anticipated by at least those X references of the IPER, see in particular 8 independent references as submitted in the IDS and thus the technical feature compound does not define a contribution over the prior art. Further, it was pointed out that under 37 CFR 1.475 the

allowed categories are not inclusive of multiple methods of use of the same special technical feature. Applicants argument is substantially that the multiple methods themselves form the special technical feature of the invention. However, the methods differ as claimed, i.e., methods of modulating neural activity in different ways and methods of treating various diseases, any one of which may or may not be enabled, anticipated or obvious over the prior art. In the methods claims the preambles are asserted weight and thus the very recitations differ in scope of treatment effects which address different mechanisms, amounts, locales of administration, numbers of doses, and in particular patient populations and outcomes. Alzheimer's disease and Parkinson's differ substantially in the etiology based on neuritic amyloid plaques and the death of cholinergic forebrain neurons, respectively. Neither possess a clear link with for example renal blood flow which is similarly recited in the claims. As the methods clearly differ in steps and outcomes the examiner finds no basis to assert that the separate uses are "linked" and is unaware of any provision for the linkage of separate methods of use when such methods are clearly distinct and the technical feature (treatment compound) lacks unity. It is noted that applicants have failed to delineate those biological activities and conditions which they believe to be shared and provide the proposed basis for such "linked unity". Thus, the separate, arguably "new" "uses" fail to delineate a single general inventive concept.

The requirement is still deemed proper as set forth in Paper No. 9, mailed 3-2-01, and made FINAL therein.

5. Applicant's conditional petition of the restriction requirement is not proper. If applicant's wish to file a formal petition they should do so in a separate paper in response to this Office Action with the requisite fee.

6. Claims 2-3, 6-9 and 11-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

7. Newly submitted claims 18 to the exent of nonelected species and claims 25-27 are directed to inventions and species that are independent or distinct from the invention originally claimed for the following reasons: As set forth in the original restriction requirement the method of modulating neuronal activity (claim 18) and method of treating disease (claim 25) are distinct. In addition, it is noted that applicant's new claims and originally presented claims are drawn to multiple biological activities and conditions which were set forth as distinct species. The biological activities and conditions are restricted in accordance with the original requirement and examination is limited to the elected species of modifying learning and facilitating memory retrieval.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 18 and 25 to the extent drawn to treating disease and to functions or activities other than facilitating learning and memory retrieval are withdrawn from

8. As a result of applicants amendment, all rejections not reiterated herein have been withdrawn by the examiner.

Priority

9. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Australia on 7-9-1996. It is noted, however, that applicant has not filed a certified copy of the PO0893 application as required by 35 U.S.C. 119(b). Prior art is applied accordingly.

Rejections Necessitated by Amendment

Claim Objections

10. Claims 18 and 25 are objected to as being drawn to a non-elected invention and reciting non-elected species of biological activity.

11. Claims 22-23 and 25 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Here claims 22-23 which depend from claim 18 do not further limit because the methods of administration are not clearly altered in any way. For example, by the recitation of prophylactic is the administration intended to be prior to some designated time point? Similarly by the recitation of therapeutic is the administration intended to be after some designated time point? It is noted that claims 25 is withdrawn and will not be further examined on the merits for the reasons set forth above. However, it is noted that this

claim also does not further limit the recitation of claim 18 as no disease or condition is specified and thus no further limitation as to the administration of the compound can be discerned.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 18-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite a method of modulating neuronal activity comprising administering "an effective amount for modulating neuronal activity." Yet such recitation is circular and fails to delineate any specific neuronal activity which is to be effected, amount which is sufficient or test for ascertaining such. The artisan recognizes multiple neuronal activities but fails to recognize any particular effect or effective amount which results in the method of the claim and thus until such neuronal activity is delineated the skilled artisan cannot readily discern the metes and bounds of the claim. Applicants appear to refer to the recited biological activities claimed as neuronal activities but the recitation lack sufficient antecedent basis to complete a relative clarification of the effective amount required.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

15. Claims 18-23 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Anderson et al., US 5599907, issued February 4, 1997 with a 102(e) date of May 9, 1994.

The claims are directed to administration where the effective amounts or dosages cannot be discerned as claimed. Anderson et al., teach production and use of multimeric hemoglobins in a method of supplementing oxygen carrying capacity of blood by administration to a human patient a composition of hemaglobin comprising peptide of SEQ ID Nos 19 and 20, residues 32-41 with 100% identity to the instantly claimed peptide comprising SEQ ID NO:1, see in particular abstract, claims 3, 5, 7, 12, 14, 33, 35, 38, 42-44, 54, 63 and 72-74, including a pharmaceutically acceptable carrier, including a globin domain, a cross linker, K_2HPO_4, HEPES/NaCl, see in particular Reference Examples A and B. As the instantly claimed method merely comprises administration of the peptide comprising SEQ ID NO:1, the recited properties of modulating neuronal activity i.e., motor neuron activity, cholinergic neuron activity, neuronal development and the modulation of learning and memory and facilitating memory retrieval are inherently encompassed by Anderson. Because the methods as claimed are the same, the effects necessarily flow, absent convincing factual evidence to the contrary. Something which is old does not become patentable by the discovery of a new property, see MPEP 2112. There is no

distinguishing method step claimed which has been shown to be different from Anderson and until the effective amount is discerned the instantly cliaimed method and the method of Anderson are the same. Thus, the burden of proof is upon applicant to show a difference in the method which would lead to a non-obvious property. Thus, the reference teachings anticipate the claimed invention.

16. Claims 18-23 are rejected under 35 U.S.C. 102(e) as being anticipated by Wolpe et al., US 5861483, issued January 19, 1999 and filed April 3, 1996.

Wolpe et al., teach production of a peptide inhibitor of stem cell proliferation and uses thereof in methods of inhibiting stem cell proliferation, for bone marrow transplantation, treatment of hypoproliferative disorders, treatment for tumors or patients undergoing chemotherapy, and gene transfer comprising administration of a composition comprising the peptide of SEQ ID Nos 4 and 26, residues 1-10 which share 100% identity to the instantly claimed peptide comprising SEQ ID NO:1, see in particular columns 4-5, column 8, lines 47-63 and example 17, including administration with pharmaceutically acceptable carriers and via injection, see in particular column 16, lines 13-57. As the instantly claimed method merely comprises administration of the peptide comprising SEQ ID NO:1, the recited properties of modulating neuronal activity i.e., motor neuron activity, cholinergic neuron activity, neuronal development and the modulation of learning and memory and facilitating memory retrieval are inherently encompassed by Wolpe. Because the methods as claimed are the same, the effects necessarily flow, absent convincing factual evidence to the contrary. Something which is old

does not become patentable by the discovery of a new property, see MPEP 2112. There is no distinguishing method step claimed which has been shown to be different from Wolpe and until the effective amount is discerned the instantly claimed method and the method of Wolpe are deemed the same. Thus, the burden of proof is upon applicant to show a difference in the method which would lead to a non-obvious property. Thus, the reference teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al., as set forth above, Kandel et al., Principles in Neural Science, Elsevier, 1991, pp. 1056-57 and Relton et al., J. of Exp. Med., 1991 Aug., 174(2):305-10.

Anderson et al., as set forth above teach a method of supplementing the oxygen carrying capacity of blood by administration of multimeric hemoglobin polypeptides which correspond to the instantly claimed polypeptide comprising SEQ ID NO:1.

Anderson et al., do not teach the administration via intracerebral injection.

Kandel et al., teach the prominence of the blood-brain barrier in restricting peptides and other large molecules from entering the brain and CNS.

Relton et al., teach pathogenesis associated with ischemia, caused by insufficient blood supply and delivery of oxygen to the brain. Relton et al., teach that Lipocortin-1 is a suitable peptide for inhibiting this inflammatory injury associated with ischemia. Relton et al., recognize the blood brain barrier as is recognized in the art and as is taught in Kandel. Therefore, Relton et al., choose administration via intracerebroventricular injection in order to bypass the blood brain barrier and achieve drug delivery to the brain at the site of ischemia where lipocortin functions to inhibit infarct size by decreasing inflammation.

Thus given Relton's teachings of the need to increase oxygen delivery to the brain during infarct or ischemia, the skilled artisan would be motivated to modify the administration of Anderson's compound by intracerebral injection to deliver the multimeric hemoglobin of Anderson to the brain and abrogate the detrimental effects of oxygen deprivation. The skilled artisan would recognize, as is recognized in the art and taught by Kandel, the need to circumvent the blood brain barrier in order to achieve drug delivery at the ischemic site, in the brain. As recognized and exemplified by Relton, the most common and easily employed method for achieving drug delivery to the brain is by direct intracerebral injection. The skilled artisan would have a reasonable expectation of increasing the oxygen delivered to the brain using this modified approach based on the ease and efficiency of direct intracerebral injection and the delivery of Anderson's compound which is known to supplement the oxygen carrying capacity in the blood.

Therefore, it would have been prima facie obvious for the skilled artisan, at the time of the invention, to modify Anderson's administration with intracerebral injection as taught by the

cumulative reference teachings. One of skill in the art would be motivated to do so in order to supplement oxygen in the brain at the site of infarct or ischemic disease.

19. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wolpe et al., as set forth above, Kandel et al., Principles in Neural Science, Elsevier, 1991, pp. 1056-57 and Wilkinson et al., Neurosurgery, 1994 April, 34(4):665-68.

Wolpe et al., as set forth above teach inhibitors of stem cell proliferation and a method of treating tumors or patients undergoing chemotherapy by administration of the composition, which corresponds to the instantly claimed polypeptide comprising SEQ ID NO:1.

Wolpe et al., do not teach the administration via intracerebral injection.

Kandel et al., teach the prominence of the blood-brain barrier in restricting peptides and other large molecules from entering the brain and CNS.

Wilkinson et al., teach synergistic effects of methotrexate and radiation therapy for the treatment of rat gliosarcoma brain tumors. However, Wilkinson et al., also teach that in these studies systemic toxicity and poor brain penetration (due to the blood brain barrier) of methotrexate were problematic. Wilkinson et al., teach that intracerebral injections of low dose methotrexate to the site of the tumor were able to overcome both these problems and caused significant prolongation of survival in animals.

Thus, given Wolpe's teachings of the need to inhibit cell proliferation in tissues while treating tumors in patients or in patients undergoing chemotherapy, the skilled artisan would be motivated to modify the administration of Wolpe's compound by intracerebral injection to

deliver the inhibitor of stem cell proliferation brain and abbrogate the detrimental effects of associated with tumors and tumor treatment via chemotherapy. The skilled artisan would recognize, as is recognized in the art and taught by Kandel, the need to circumvent the blood brain barrier in order to achieve drug delivery at the brain tumor site. As recognized and exemplified by Wilkinson, the most common and easily employed method for achieving drug delivery to the brain is by direct intracerebral injection. The skilled artisan would have a reasonable expectation of inhibiting stem cell proliferation in the brain using this modified approach based on the ease and efficiency of direct intracerebral injection and the delivery of Wolpe's compound which is known to inhibit stem cell proliferation.

Therefore, it would have been prima facie obvious for the skilled artisan,at the time of the invention, to modify Wolpe's administration with intracerebral injection as taught by the cumulative reference teachings. One of skill in the art would be motivated to do so in order to inhibit stem cell proliferation during treatment of the brain tumor.

Status of Claims

20. No claims are allowed.

Conclusion

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

22. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
October 17, 2001

CHRISTINE J. SAOUD
PRIMARY EXAMINER

Christine J. Saoud